

FILE 'HOME' ENTERED AT 13:06:17 ON 13 JUL 2001

=> fil reg

=> s cetorelix/cn

L1 1 CETRORELIX/CN

=> d

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS

RN 120287-85-6 REGISTRY

CN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ornithyl-L-leucyl-L-arginyl-L-prolyl- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 3: PN: W00018423 PAGE: 26 claimed protein

CN **Cetorelix**

FS PROTEIN SEQUENCE; STEREOSEARCH

DR 126299-94-3

MF C70 H92 Cl N17 O14

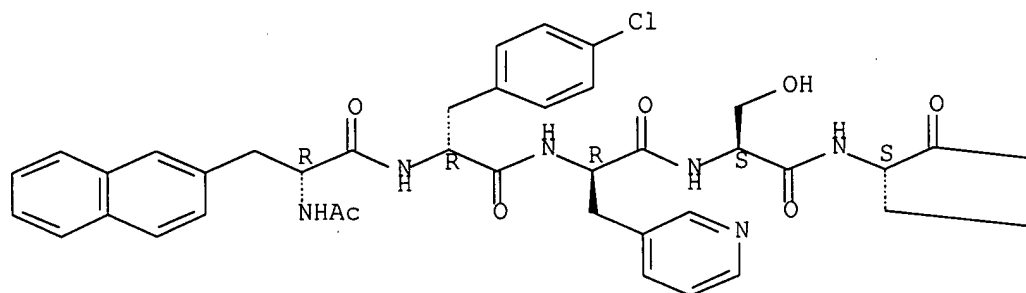
CI COM

SR CA

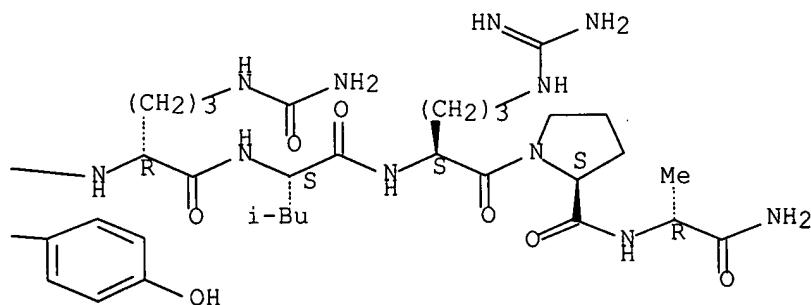
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK\*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL  
(\*File contains numerically searchable property data)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



141 REFERENCES IN FILE CA (1967 TO DATE)

6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

142 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> fil medline caplus embase biosis uspatfull

=> s 11 or cetrorelix

L2 777 L1 OR CETRORELIX

=>

=>

=>

=> s endometri? and 12

L3 78 ENDOMETRI? AND L2

=> dup rem 13

PROCESSING COMPLETED FOR L3

L4 51 DUP REM L3 (27 DUPLICATES REMOVED)

=> s 14 range=,1999

',1999' IS NOT A VALID RANGE FOR FILE 'MEDLINE'

Valid RANGE values are file specific. For more information, enter  
HELP RANGE or HELP SET RANGE at an arrow prompt (=>) in the current  
file.

ENTER RANGE FOR FILE 'MEDLINE' OR (ALL):end

SEARCH ENDED BY USER

L5 19 L4

=>

=> s 14 not py>1999

L6 21 L4 NOT PY>1999

=> d ibib abs kwic tot

L6 ANSWER 1 OF 21 MEDLINE

ACCESSION NUMBER: 2000149595 MEDLINE

DOCUMENT NUMBER: 20149595 PubMed ID: 10685334

TITLE: LH-RH analogues: I. Their impact on reproductive medicine.

AUTHOR: Schally A V

CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans  
Affairs Medical Center, New Orleans, Louisiana 70112-1262,  
USA.

CONTRACT NUMBER: AM-09094 (NIADDK)

CA-40003 (NCI)

DK-07467 (NIDDK)

+

SOURCE: GYNECOLOGICAL ENDOCRINOLOGY, (1999 Dec) 13 (6) 401-9. Ref:  
81

Journal code: 125; 8807913. ISSN: 0951-3590.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000327

Last Updated on STN: 20000327

Entered Medline: 20000310

AB In the 28 years that have passed since the elucidation of the structure of  
luteinizing hormone-releasing hormone (LH-RH), diverse clinical  
applications in the field of reproductive medicine and related fields have  
been established for agonists of LH-RH, based on inhibition of the  
pituitary-gonadal axis. Various clinical investigations with agonists of  
LH-RH in benign gynecologic disorders, polycystic ovary disease (PCOD), in  
vitro fertilization-embryo transfer (IVF-ET), benign prostatic hypertrophy  
(BPH), precocious puberty and contraception were reviewed. LH-RH  
antagonists inhibit LH, follicle-stimulating hormone (FSH), and sex  
steroid secretion immediately after their administration and thus achieve  
rapid therapeutic effects. LH-RH antagonists should find applications in  
the treatment of uterine leiomyomas, endometriosis, and in  
controlled ovarian stimulation-assisted reproductive techniques (COS-ART),  
which have been already established for the agonists. Modern LH-RH  
antagonists such as cetrorelix may prove superior to the

agonists in COS-ART and also in the treatment of BPH, but additional studies in these and other areas are needed.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.  
Contraception  
Endometriosis: DT, drug therapy  
\*Gonadorelin: AA, analogs & derivatives  
Polycystic Ovary Syndrome: DT, drug therapy  
Prostatic Hyperplasia: DT, drug therapy

L6 ANSWER 2 OF 21 MEDLINE

ACCESSION NUMBER: 2000037969 MEDLINE  
DOCUMENT NUMBER: 20037969 PubMed ID: 10573298  
TITLE: Luteinizing hormone-releasing hormone analogs: their impact on the control of tumorigenesis.  
AUTHOR: Schally A V  
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, and Department of Medicine, Tulane University School of Medicine, New Orleans, LA 70112, USA.  
CONTRACT NUMBER: AM-09094 (NIADDK)  
CA-40003 (NCI)  
DK-07467 (NIDDK)  
+  
SOURCE: PEPTIDES, (1999) 20 (10) 1247-62. Ref: 185  
Journal code: PA7; 8008690. ISSN: 0196-9781.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199912  
ENTRY DATE: Entered STN: 20000113  
Last Updated on STN: 20000113  
Entered Medline: 19991223

AB The development of the luteinizing hormone-releasing hormone (LH-RH) agonists and antagonists and the principles of their clinical use were reviewed. In the 28 years that have elapsed since the elucidation of the structure of LH-RH, various applications in gynecology, reproductive medicine, and oncology have been established for LH-RH agonists and antagonists. These clinical applications are based on inhibition of the pituitary and the gonads. The advantage of the LH-RH antagonists is due to the fact that they inhibit the secretion of gonadotropins and sex steroids immediately after the first injection and thus achieve rapid therapeutic effects in contrast to the agonists, which require repeated administration. LH-RH antagonists should find applications in the treatment of benign gynecologic disorders and benign prostatic hypertrophy and in assisted reproduction programs. The primary treatment of advanced androgen-dependent prostate cancer is presently based on the use of depot preparations of LH-RH agonists, but antagonists like **Cetrorelix** already have been tried successfully. Antagonists of LH-RH might be more efficacious than agonists in treatment of patients with breast cancer as well as ovarian and endometrial cancer. Recently, practical cytotoxic analogs of LH-RH that can be targeted to LH-RH receptors on tumors have been synthesized and successfully tested in experimental cancer models. Targeted cytotoxic LH-RH analogs show a great promise for therapy of prostate, breast, and ovarian cancers.

L6 ANSWER 3 OF 21 MEDLINE

ACCESSION NUMBER: 96077434 MEDLINE  
DOCUMENT NUMBER: 96077434 PubMed ID: 8567825  
TITLE: Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of infertility: an overview.  
AUTHOR: Reissmann T; Felberbaum R; Diedrich K; Engel J; Comaru-Schally A M; Schally A V  
CORPORATE SOURCE: Clinic for Obstetrics and Gynaecology, University of Lubeck, Germany.  
SOURCE: HUMAN REPRODUCTION, (1995 Aug) 10 (8) 1974-81. Ref: 62  
Journal code: HRP; 8701199. ISSN: 0268-1161.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199603  
ENTRY DATE: Entered STN: 19960315  
Last Updated on STN: 19960315  
Entered Medline: 19960307

AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohipophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible new approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

CT Check Tags: Female; Human  
Adult  
Amino Acid Sequence  
Endometriosis: DT, drug therapy  
Gonadorelin: AG, agonists  
\*Gonadorelin: AI, antagonists & inhibitors  
Gonadorelin: PH, physiology  
Infertility, Female: PP, physiopathology  
\*Infertility, . . .

L6 ANSWER 4 OF 21 MEDLINE

ACCESSION NUMBER: 94127534 MEDLINE  
DOCUMENT NUMBER: 94127534 PubMed ID: 8296852  
TITLE: Direct growth inhibition of human **endometrial** cancer cells by the gonadotropin-releasing hormone antagonist SB-75: role of apoptosis.  
AUTHOR: Kleinman D; Douvdevani A; Schally A V; Levy J; Sharoni Y  
CORPORATE SOURCE: Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Soroka Medical Center of Kupat Holim, Beer-Sheva, Israel.  
SOURCE: AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1994 Jan) 170 (1 Pt 1) 96-102.  
Journal code: 3NI; 0370476. ISSN: 0002-9378.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199403  
ENTRY DATE: Entered STN: 19940314  
Last Updated on STN: 19970203  
Entered Medline: 19940301

AB OBJECTIVE: Our objective was to study the direct action of the gonadotropin-releasing hormone antagonist SB-75 and the agonist buserelin on the proliferation of **endometrial** cancer cells. STUDY DESIGN: Two human **endometrial** cell lines that differ in histologic subtype and estrogen receptor content were treated with gonadotropin-releasing hormone analog. We measured the number of viable cells, cell cycle parameters, and apoptotic processes. RESULTS: Growth of the Ishikawa cells was inhibited by SB-75 in a dose-dependent manner. 17 beta-Estradiol partially abolished the inhibitory effect of SB-75. The

growth of the HEC-1A cells was not affected by the antagonist. Neither **endometrial** cancer cell line showed significant sensitivity to the agonist buserelin. Tenfold concentration of the gonadotropin-releasing hormone agonist did not abolish the inhibitory effect of the antagonist on cell growth. The growth inhibition was not associated with any change in cell cycle parameters but was associated with an induction of apoptosis. CONCLUSION: The gonadotropin-releasing hormone antagonist SB-75 directly inhibits the growth of some human **endometrial** cancer cells and thus may be suitable for the treatment of **endometrial** tumors.

TI Direct growth inhibition of human **endometrial** cancer cells by the gonadotropin-releasing hormone antagonist SB-75: role of apoptosis. suitable for the treatment of **endometrial** tumors.

CT . . .

Division: DE, drug effects

DNA, Neoplasm: AN, analysis

DNA, Neoplasm: IP, isolation & purification

Dose-Response Relationship, Drug

Electrophoresis, Agar Gel

**Endometrial Neoplasms: CH, chemistry**

**\*Endometrial Neoplasms: DT, drug therapy**

**Endometrial Neoplasms: PA, pathology**

Estradiol: PD, pharmacology

Flow Cytometry

\*Gonadorelin: AA, analogs & derivatives

\*Gonadorelin: AI, antagonists & inhibitors

Gonadorelin: . . .

RN 120287-85-6 (SB 75); 33515-09-2 (Gonadorelin); 50-28-2 (Estradiol); 57982-77-1 (Buserelin)

L6 ANSWER 5 OF 21 MEDLINE

ACCESSION NUMBER: 94089967 MEDLINE

DOCUMENT NUMBER: 94089967 PubMed ID: 8265821

TITLE: Regulation of **endometrial** cancer cell growth by insulin-like growth factors and the luteinizing hormone-releasing hormone antagonist SB-75.

AUTHOR: Kleinman D; Roberts C T Jr; LeRoith D; Schally A V; Levy J; Sharoni Y

CORPORATE SOURCE: Clinical Biochemistry Department, Faculty of Health Sciences, Ben-Gurion University of the Negev, Soroka Medical Center of Kupat Holim, Beer-Sheva, Israel.

SOURCE: REGULATORY PEPTIDES, (1993 Oct 20) 48 (1-2) 91-8. Journal code: RBB; 8100479. ISSN: 0167-0115.

PUB. COUNTRY: Netherlands  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199401

ENTRY DATE: Entered STN: 19940209

Last Updated on STN: 19970203

Entered Medline: 19940127

AB The involvement of IGFs in growth regulation of the Ishikawa **endometrial** tumor cell line and the possible interference of LH-RH analogues with a potential autocrine or paracrine loop involving IGFs was evaluated. The mitogenic effects of IGF-I, IGF-II, and insulin were compared. IGF-I was found to be 3-fold more potent than IGF-II and 30-fold more potent than insulin, suggesting that the effects of these growth factors are mediated by the IGF-I receptor. Ishikawa **endometrial** cancer cells secrete IGF-II, but not IGF-I, and insulin (1 microM) stimulates IGF-II release. The LH-RH antagonist [Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal(3)3, D-Cit6, D-Ala10]-GnRH (SB-75, **CETRORELIX**) inhibited basal and IGF-induced growth. Moreover, this antagonist almost completely inhibited IGF-II release from Ishikawa cells, while having no significant effect on the number or affinity of IGF-I binding sites. Inhibition of IGF-II release occurred at a lower SB-75 concentration than that needed for a reduction in cell number. The ED50 of SB-75 for IGF-II release was 0.3 microM as compared to 1.5 microns concentration which is required for reduction in cell number, suggesting that inhibition of growth factor release precedes cell growth inhibition. We conclude that the LH-RH antagonist SB-75 can inhibit the growth of **endometrial** cancer cells by interfering with the autocrine action of IGF-II and also by directly inhibiting the growth-stimulatory effects of IGFs, probably through effects on a post-receptor mechanism.

TI Regulation of **endometrial** cancer cell growth by insulin-like

growth factors and the luteinizing hormone-releasing hormone antagonist SB-75.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't

\*Cell Division: DE, drug effects

Cell Line

Dose-Response Relationship, Drug

Drug Interactions

Endometrial Neoplasms

\*Gonadorelin: AA, analogs & derivatives

\*Gonadorelin: AI, antagonists & inhibitors

Gonadorelin: PD, pharmacology

\*Insulin: PD, pharmacology

\*Insulin-Like Growth. . .

RN 11061-68-0 (Insulin); 120287-85-6 (SB 75); 33515-09-2

(Gonadorelin); 67763-96-6 (Insulin-Like Growth Factor I); 67763-97-7

(Insulin-Like Growth Factor II)

L6 ANSWER 6 OF 21 MEDLINE

ACCESSION NUMBER: 94086728 MEDLINE

DOCUMENT NUMBER: 94086728 PubMed ID: 8263128

TITLE: High affinity binding and direct antiproliferative effects of luteinizing hormone-releasing hormone analogs in human endometrial cancer cell lines.

AUTHOR: Emons G; Schroder B; Ortmann O; Westphalen S; Schulz K D; Schally A V

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Philipps University, Marburg, Germany.

SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1993 Dec) 77 (6) 1458-64.

Journal code: HRB; 0375362. ISSN: 0021-972X.

PUB. COUNTRY: United States

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199401

ENTRY DATE: Entered STN: 19940209

Last Updated on STN: 19970203

Entered Medline: 19940124

AB Although specific binding sites for LH-releasing hormone (LHRH) and its analogs have been demonstrated in biopsy samples of human endometrial cancer, their biological significance remains obscure. In this study we evaluated whether binding sites for LHRH are also present in the human endometrial cancer cell lines HEC-1A and Ishikawa and if such sites could mediate antiproliferative effects of LHRH analogs. Using [125I,D-Trp6]LHRH as a ligand, a high affinity/low capacity binding site was detected in both lines: HEC-1A line, dissociation constant (Kd)1 =  $5.7 \times 10^{-9}$  mol/L, binding capacity (Bmax)1 = 78 fmol/10(6) cells; Ishikawa line, Kd1 =  $4.2 \times 10^{-9}$  mol/L, Bmax1 = 29 fmol/10(6) cells. In addition, a second class of low affinity/high capacity binding sites for LHRH was demonstrated (HEC-1A line, Kd2 =  $1.4 \times 10^{-6}$  mol/L, Bmax2 = 21 pmol/10(6) cells; Ishikawa, Kd2 =  $4 \times 10^{-6}$  mol/L, Bmax2 = 32 pmol/10(6) cells). In the presence of  $10^{-5}$  mol/L agonist [D-Trp6]LHRH (triptorelin), the proliferation of HEC-1A and Ishikawa cell lines was significantly reduced to 76 +/- 2% and 88 +/- 4% of controls, respectively, after 24 h and to 64 +/- 2% and 62 +/- 2%, respectively, after 6 days. Dose-response experiments showed that lower concentrations ( $10^{-9}$  mol/L) of the agonist decreased the proliferation to 80 +/- 1% for the HEC-1A line and 71 +/- 2% of controls for the Ishikawa line after 6 days. Antiproliferative effects are enhanced by increasing the doses of triptorelin and were maximal in this series of experiments at  $10^{-5}$  mol/L, the proliferation in the HEC-1A line being 62 +/- 1% and in the Ishikawa line 52 +/- 2% of controls, respectively. Similar time- and dose-dependent antiproliferative effects were obtained in both cell lines with the LHRH antagonist SB-75 (cetrorelix). These data suggest that LHRH analogs can directly inhibit the proliferation of human endometrial cancer cells in vitro. This direct action could be mediated through the high affinity LHRH binding sites.

TI High affinity binding and direct antiproliferative effects of luteinizing hormone-releasing hormone analogs in human endometrial cancer cell lines.

CT . . . Female; Human; Support, Non-U.S. Gov't

Amino Acid Sequence

Binding Sites

Cell Division: DE, drug effects  
Dose-Response Relationship, Drug  
Drug Stability  
\*Endometrial Neoplasms: DT, drug therapy  
Endometrial Neoplasms: ME, metabolism  
Endometrial Neoplasms: PA, pathology  
\*Gonadorelin: AA, analogs & derivatives  
\*Gonadorelin: AI, antagonists & inhibitors  
Gonadorelin: ME, metabolism  
Gonadorelin: PD, pharmacology

RN 120287-85-6 (SB 75); 33515-09-2 (Gonadorelin); 57773-63-4  
(Triptorelin)

L6 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:200802 CAPLUS

DOCUMENT NUMBER: 128:268963

TITLE: Presence and characteristics of receptors for  
[D-Trp6]luteinizing hormone releasing hormone and  
epidermal growth factor in human ovarian cancer  
AUTHOR(S): Srkalovic, Gordan; Schally, Andrew V.; Wittliff, James  
L.; Day, Thomas G., Jr.; Jenison, Eric L.

CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans  
Affairs Medical Center and Department of Medicine,  
Tulane University Medical School, New Orleans, LA, USA

SOURCE: Int. J. Oncol. (1998), 12(3), 489-498

CODEN: IJONES; ISSN: 1019-6439

PUBLISHER: International Journal of Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study was undertaken to establish the presence and characteristics of  
receptors for [D-Trp6]LH-RH on the membranes of human ovarian cancer.  
Specific binding of [<sup>125</sup>I, D-Trp6]LH-RH was found in 29 of 37 (78.4%)  
ovarian cancers and in 6 of 11 (54.5%) non-malignant human ovaries.  
Ligand binding was dependent on time and plasma membrane concn. in a  
fashion expected of a peptide hormone. Satn., kinetic and displacement  
data were consistent with the presence of a highly specific, single class  
of non-cooperative binding site. On the basis of receptors affinity,  
LH-RH-receptor-pos. ovarian cancers could be divided into two groups: high  
affinity group (Kd=2.71+-0.60 nM; Bmax=0.46+-0.07 pmol/mg membrane  
protein) comprising 55% of tumors, and low affinity group (Kd=78.0+-19.6  
nM; Bmax=9.44+-2.68 pmol/mg membrane protein) which included 45% of  
tumors. LH-RH antagonist Cetrorelix showed an affinity to LH-RH  
receptors on ovarian cancers 14 times higher than the agonist  
[D-Trp6]LH-RH. Using <sup>125</sup>I-epidermal growth factor, specific high affinity  
receptors were also detected in membranes from 13 of 24 (54%) ovarian  
cancers and 5 of 11 (45%) non-malignant ovaries. The demonstration of  
LH-RH receptors in human ovarian cancers provides a rationale for the use  
of therapeutic approaches based on LH-RH analogs in this malignancy. The  
probable involvement of growth factors in the development of ovarian  
cancers suggests the merit of trying a combined therapy based on analogs  
of LH-RH and somatostatin for this carcinoma.

IT Antitumor agents

Endometrial adenocarcinoma

Ovarian carcinoma

(LH-RH receptors and EGF receptors characterization in human ovarian  
cancer cells)

IT 120287-85-6, Cetrorelix

RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
process); BIOL (Biological study); PROC (Process)

(LH-RH receptors and EGF receptors characterization in human ovarian  
cancer cells)

L6 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:29519 CAPLUS

DOCUMENT NUMBER: 128:162903

TITLE: Antagonistic analogs of LHRH in oncology and  
gynecology

AUTHOR(S): Schally, A. V.; Comaru-Schally, A. M.;  
Gonzalez-Barcena, D.; Reissmann, T.; Engel, J.

CORPORATE SOURCE: UK

SOURCE: Int. Congr., Symp. Semin. Ser. (1997),  
13(Endometriosis Today), 401-413

CODEN: ICGSEM; ISSN: 0969-2622  
PUBLISHER: Parthenon Publishing Group Ltd.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
AB A review with 70 refs. LHRH antagonists, esp. **cetrorelix**, are reviewed along with their prospective clin. applicability to in vitro fertilization/embryo transfer, gynecol. oncol., fibroids, **endometriosis** and prostate disorders.

L6 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:707016 CAPLUS  
DOCUMENT NUMBER: 128:18709  
TITLE: Rational use of agonists and antagonists of luteinizing hormone-releasing hormone (LH-RH) in the treatment of hormone-sensitive neoplasms and gynecologic conditions  
AUTHOR(S): Schally, Andrew V.; Maria Comaru-Schally, Ana  
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, VA Medical Centre and Section of Experimental Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, USA  
SOURCE: Adv. Drug Delivery Rev. (1997), 28(1), 157-169  
CODEN: ADDREP; ISSN: 0169-409X  
PUBLISHER: Elsevier  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review, with 89 refs. Analogs of LH-releasing hormone (LH-RH) have made possible new approaches to the treatment of some hormone-dependent cancers and diseases and conditions which result from inappropriate sex hormone levels. In the fields of both gynecol. and oncol., the development of sustained delivery depot systems has played a key role in the clin. use of LH-RH agonists and will be also essential for the LH-RH antagonists. Clin. show that therapy with agonists of LH-RH is the preferred method of treatment for men with advanced prostate cancer. For prostate cancer and other indications, the new LH-RH antagonists such as **Cetrorelix** may offer an advantage based on the fact that they inhibit LH, FSH and sex-steroid secretion from the start of the administration and thus reduce the time of the onset of therapeutic effects. The use of antagonists would avoid the temporary clin. "flare-up" of the disease which can occur with the agonists in men with prostate cancer. The rapid shrinkage of the prostate and improvement in urinary symptoms obtained with **Cetrorelix** in men with benign prostatic hyperplasia (BHP) suggests that LH-RH antagonists offer a therapeutic alternative in patients who are considered poor surgical risks. Various exptl. and clin. studies suggest that analogs of LH-RH might be useful for treatment of premenopausal women with estrogen-dependent breast cancer. LH-RH antagonists such as **Cetrorelix** could be also considered for hormonal therapy of epithelial ovarian cancer which responds only marginally to the agonists, and for treatment of **endometrial** cancer. Many investigators have reported beneficial effects of LH-RH agonists in the treatment of patients with leiomyomas. LH-RH antagonists also appear to be promising for therapy of uterine leiomyomas, and in addn. might be useful for treatment of **endometriosis** and polycystic ovarian disease (PCOD). LH-RH agonists have been employed in in vitro fertilization and embryo transfer (IVF-ET) programs to prevent a premature rise in LH and various results suggest that the use of antagonist **Cetrorelix** in assisted reprodn. procedures, could be even more advantageous. For most of these indications, the use of sustained release depot prepns. will be required.

L6 ANSWER 10 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998243707 EMBASE  
TITLE: Effects of LHRH-analogues on mitogenic signal transduction in cancer cells.  
AUTHOR: Emons G.; Muller V.; Ortmann O.; Schulz K.-D.  
CORPORATE SOURCE: G. Emons, Dept. of Obstetrics and Gynecology, Philipps University, Pilgrimstein 3, D-35033 Marburg, Germany  
SOURCE: Journal of Steroid Biochemistry and Molecular Biology, (1998) 65/1-6 (199-206).  
Refs: 58  
ISSN: 0960-0760 CODEN: JSBBEZ  
PUBLISHER IDENT.: S 0960-0760(97)00189-1  
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 016 Cancer  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB The expression of luteinizing hormone-releasing hormone (LHRH) and its receptors has been demonstrated in a number of human malignant tumors, including cancers of the breast, ovary, **endometrium** and prostate. These findings suggest the presence of an autocrine regulatory system based on LHRH. Recent studies in our laboratory have demonstrated that the function of LHRH produced by ovarian cancer cells is the inhibition of their proliferation. Dose-dependent antiproliferative effects of LHRH-agonists have been observed by several laboratories in cell lines derived from the above cancers. Interestingly, also LHRH-antagonists have marked antiproliferative activity in most of the ovarian, breast and **endometrial** cancer cell lines tested so far, indicating that the dichotomy of LHRH-agonists/LHRH- antagonists is not valid for the LHRH-system in cancer cells. In addition, our data suggest that the classical LHRH receptor signal transduction mechanisms known from the pituitary (phospholipase-C, protein kinase C, adenylyl cyclase) are not involved in the mediation of LHRH effects in cancer cells. Data obtained by several groups, including ours, rather suggest that EaRn analogs interfere with the signal transduction of growth-factor receptors and related oncogene products associated with tyrosine-kinase activity. The mechanism of action is probably an LHRH-induced activation of a phosphotyrosine phosphatase, counteracting the effects of receptor associated tyrosine kinase. In our hands, LHRH analogs virtually blocked the EGF- induced MAP-kinase activity of ovarian and **endometrial** cancer cells. The pharmacological exploitation of this mechanism might provide promising new therapies for these cancers.

CT Medical Descriptors:  
\*hormonal regulation  
\*cancer cell: ET, etiology  
cell proliferation  
dose response  
ovary cancer: ET, etiology  
breast cancer: ET, etiology  
**endometrium cancer: ET, etiology**  
signal transduction  
drug mechanism  
human  
human cell  
conference paper  
\*gonadorelin derivative: PD, pharmacology  
\*gonadorelin agonist: PD, pharmacology  
\*protirelin: PD, pharmacology  
\*gonadorelin receptor: EC, endogenous compound  
phospholipase c: EC, endogenous compound  
protein kinase c: EC, endogenous compound  
adenylate cyclase: EC, endogenous compound  
protein tyrosine phosphatase: EC, endogenous compound  
**cetrorelix: PD, pharmacology**

RN (protirelin) 24305-27-9; (phospholipase c) 9001-86-9; (protein kinase c) 141436-78-4; (adenylate cyclase) 9012-42-4; (protein tyrosine phosphatase) 79747-53-8, 97162-86-2; (**cetrorelix**) 120287-85-6

L6 ANSWER 11 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998054546 EMBASE  
TITLE: Gonadotropin-releasing hormone and analogues in reproductive medicine.  
AUTHOR: Cardamakis E.; Tzingounis V.; Keramida M.  
CORPORATE SOURCE: Dr. V. Tzingounis, Department of Obstetrics/Gynecology, Medical School of Univ. of Patras, 265 10 Patra, Greece  
SOURCE: Review of Clinical Pharmacology and Pharmacokinetics, International Edition, (1997) 11/2-3 (97-103).  
Refs: 56  
ISSN: 1011-6583 CODEN: EKIEE2  
COUNTRY: Greece  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 010 Obstetrics and Gynecology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: English

CT Medical Descriptors:

\*endometrium cancer: DT, drug therapy  
\*breast fibroma: DT, drug therapy  
\*ovary hyperstimulation  
\*endometriosis: DT, drug therapy  
female infertility: DT, drug therapy  
drug efficacy  
hormonal therapy  
osteoporosis: SI, side effect  
drug indication  
luteinizing hormone release  
follitropin release  
human  
clinical trial  
article  
\*gonadorelin: AE, adverse. . . PD, pharmacology  
\*gonadorelin derivative: AE, adverse drug reaction  
\*gonadorelin derivative: DT, drug therapy  
\*gonadorelin derivative: PD, pharmacology  
luteinizing hormone: EC, endogenous compound  
follitropin: EC, endogenous compound  
cetrorelix: DT, drug therapy  
danazol: DT, drug therapy  
triptorelin: AE, adverse drug reaction  
triptorelin: DT, drug therapy  
leuprorelin: AE, adverse drug reaction  
leuprorelin: DT, drug therapy  
buserelin: . . .

RN (gonadorelin) 33515-09-2, 9034-40-6; (luteinizing hormone) 39341-83-8,  
9002-67-9; (follitropin) 9002-68-0; (cetrorelix)  
120287-85-6; (danazol) 17230-88-5; (triptorelin) 57773-63-4;  
(leuprorelin) 53714-56-0, 74381-53-6; (buserelin) 57982-77-1; (nafarelin)  
76932-56-4; (ethinylestradiol) 57-63-6; (cyproterone acetate) 427-51-0

L6 ANSWER 12 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96139165 EMBASE

DOCUMENT NUMBER: 1996139165

TITLE: [Development strategies for drugs in the therapy of  
hormone-dependent tumors].  
ENTWICKLUNGSTRATEGIEN FUR ARZNEISTOFFE ZUR THERAPIE  
HORMONABHANGIGER TUMOREN.

AUTHOR: Von Angerer E.

CORPORATE SOURCE: Institut fur Pharmazie, Universitat Regensburg,  
Universitatsstrasse 1, D-93040 Regensburg, Germany

SOURCE: Pharmazie in Unserer Zeit, (1996) 25/2 (74-84).

ISSN: 0048-3664 CODEN: PHUZBI

COUNTRY: Germany

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology  
010 Obstetrics and Gynecology  
016 Cancer  
028 Urology and Nephrology  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: German

CT Medical Descriptors:

\*tumor: DT, drug therapy  
breast carcinoma: DT, drug therapy  
cancer chemotherapy  
endometrium carcinoma: DT, drug therapy  
female  
human  
male  
prostate carcinoma: DT, drug therapy  
review  
\*antiandrogen: DT, drug therapy  
\*antiestrogen: DT, drug therapy  
\*antigestagen: DT, drug therapy  
\*aromatase inhibitor: DT, . . . DT, drug therapy  
buserelin: DT, drug therapy  
bicalutamide: DT, drug therapy  
droloxifene: DT, drug therapy

fadrozole: DT, drug therapy  
finasteride: DT, drug therapy  
flutamide: DT, drug therapy  
    **cetrorelix: DT, drug therapy**  
goserelin: DT, drug therapy  
idoxifene: DT, drug therapy  
ketoconazole: DT, drug therapy  
letrozole: DT, drug therapy  
leuprorelin: DT, drug therapy  
n butyl 11. . .

RN. . . diol) 129453-61-8; (aminoglutethimide) 125-84-8; (anastrozole)  
120511-73-1; (atamestane) 96301-34-7; (buserelin) 57982-77-1;  
(bicalutamide) 90357-06-5; (droloxifene) 82413-20-5; (fadrozole)  
102676-31-3; (finasteride) 98319-26-7; (flutamide) 13311-84-7; (  
**cetrorelix**) 120287-85-6; (goserelin) 65807-02-5;  
(idoxifene) 116057-75-1; (ketoconazole) 65277-42-1; (letrozole)  
112809-51-5; (leuprorelin) 53714-56-0, 74381-53-6; (n butyl 11 (3,17beta  
dihydroxyestra 1,3,5(10) trien 7alpha yl). . .

L6 ANSWER 13 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95129571 EMBASE

DOCUMENT NUMBER: 1995129571

TITLE: **Cetrorelix**. D-20453 (as trifluoroacetate).  
D-20761 (as acetate). SB-75.

SOURCE: Drugs of the Future, (1995) 20/3 (299-300).  
ISSN: 0377-8282 CODEN: DRFUD4

COUNTRY: Spain

DOCUMENT TYPE: Journal; (Short Survey)

FILE SEGMENT: 010 Obstetrics and Gynecology  
016 Cancer  
028 Urology and Nephrology  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

TI **Cetrorelix**. D-20453 (as trifluoroacetate). D-20761 (as acetate).  
SB-75.

CT Medical Descriptors:

\*antineoplastic activity

**\*endometrium cancer**

\*fertilization in vitro

\*hyperplasia: DT, drug therapy

\*ovary cancer

\*prostate cancer: DT, drug therapy

drug efficacy

drug safety

**endometriosis**

female

human

male

mouse

nonhuman

ovulation

short survey

subcutaneous drug administration

tumor cell

\*gonadorelin antagonist: PD, pharmacology

\*gonadorelin antagonist: DT, drug therapy

\*gonadorelin antagonist: CM, drug comparison

**cetrorelix: PD, pharmacology**

**cetrorelix: DT, drug therapy**

**cetrorelix: CM, drug comparison**

lhrh [6 dextro tryptophan]: CM, drug comparison

unclassified drug

RN (**cetrorelix**) 120287-85-6

L6 ANSWER 14 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94237233 EMBASE

DOCUMENT NUMBER: 1994237233

TITLE: The use of luteinizing hormone releasing hormone agonists  
and antagonists in gynaecological cancers.

AUTHOR: Emons G.; Schally A.V.

CORPORATE SOURCE: Dept of Obstetrics and Gynecology, Philipps  
University, D-35037 Marburg, Germany

SOURCE: Human Reproduction, (1994) 9/7 (1364-1379).  
ISSN: 0268-1161 CODEN: HUREEE  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 010 Obstetrics and Gynecology  
016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: English  
SUMMARY LANGUAGE: English

AB The use of agonistic analogues of luteinizing hormone releasing hormone (LHRH) is an established therapy for hormone-dependent metastatic pre-menopausal breast cancer. Their mechanism of action in this disease is the suppression of ovarian oestrogen production (medical castration). In the treatment of post-menopausal metastatic breast cancer, LHRH agonists also have some effect, although minor, probably through a suppression of ovarian androgen production. Convincing evidence has been accumulated that LHRH analogues can directly inhibit the proliferation of breast cancer cells in vitro. The clinical impact of these findings, however, is still controversial. Experimental data and several pilot clinical trials suggest that in epithelial ovarian cancer and sex-cord-stromal tumours of the ovary, LHRH agonists might have antitumour activity through the suppression of gonadotrophin secretion (selective medical hypophysectomy). Phase m clinical trials, evaluating this hypothesis, are in progress. Direct antiproliferative effects of LHRH analogues on epithelial ovarian cancer cells have been demonstrated in vitro. In endometrial cancer, experimental and early clinical results support the concept of a direct antiproliferative activity of LHRH analogues. Recently, potent antagonistic analogues of LHRH, devoid of relevant side-effects have become available for clinical testing. These new antagonists might be superior to agonistic LHRH analogues with respect to the rapidity and efficacy of selective medical hypophysectomy and medical castration. Modern LHRH antagonists might also permit a better exploitation of direct antitumour effects. A further therapeutic improvement in gynaecological oncology might result from a combination of LHRH agonists or antagonists with other peptide hormone analogues such as agonists of somatostatin or antagonists of bombesin/gastrin releasing peptide which have antitumour activity. Since 50% of breast cancers and 80% of epithelial ovarian cancers and endometrial cancers have high affinity binding sites for LHRH, cytotoxic LHRH analogues might provide a targeted chemotherapy, which would be more efficacious and less toxic than conventional regimens.

CT Medical Descriptors:  
\*gynecologic . . . site  
breast cancer: DT, drug therapy  
breast metastasis: DT, drug therapy  
cancer inhibition  
cell proliferation  
clinical trial  
cytotoxicity  
depression: SI, side effect  
diabetes mellitus: SI, side effect  
drug efficacy  
drug mechanism  
    endometrium cancer: DT, drug therapy  
    endometrium cancer: RT, radiotherapy  
    endometrium cancer: SU, surgery  
estrogen synthesis  
female  
gonadotropin release  
hot flush: SI, side effect  
human  
hypertension: SI, side effect  
leydig cell tumor: DT, drug therapy  
male  
nonhuman  
obesity: SI, side effect  
ovary. . .  
releasing peptide: EC, endogenous compound  
gestagen: DT, drug therapy  
gestagen: CT, clinical trial  
gestagen: AE, adverse drug reaction  
gestagen: CB, drug combination

gonadorelin: EC, endogenous compound  
cetrorelix: CT, clinical trial  
cetrorelix: DT, drug therapy  
cetrorelix: PD, pharmacology  
goserelin: CT, clinical trial  
goserelin: PD, pharmacology  
goserelin: DT, drug therapy  
goserelin: AE, adverse drug reaction  
leuprorelin: DT, drug therapy  
leuprorelin: CT, clinical trial  
leuprorelin: . . .

RN. . . 566-48-3; (bombesin) 31362-50-2; (buserelin) 57982-77-1; (cisplatin)  
15663-27-1, 26035-31-4, 96081-74-2; (doxorubicin) 23214-92-8, 25316-40-9;  
(gastrin releasing peptide) 74815-57-9, 80043-53-4; (gonadorelin)  
33515-09-2, 9034-40-6; (cetrorelix) 120287-85-6;  
(goserelin) 65807-02-5; (leuprorelin) 53714-56-0, 74381-53-6; (tamoxifen)  
10540-29-1; (triptorelin) 57773-63-4; (vapreotide) 103222-11-3

L6 ANSWER 15 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94179320 EMBASE

DOCUMENT NUMBER: 1994179320

TITLE: Introduction of LHRH-antagonists into the treatment of  
gynaecological disorders.

AUTHOR: Reissmann Th.; Diedrich K.; Comaru-Schally A.M.; Schally  
A.V.

CORPORATE SOURCE: Clinic Obstetrics and Gynaecology, University of  
Lubeck, Lubeck, Germany

SOURCE: Human Reproduction, (1994) 9/5 (767-769).

ISSN: 0268-1161 CODEN: HUREEE

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; (Short Survey)

FILE SEGMENT: 010 Obstetrics and Gynecology  
021 Developmental Biology and Teratology  
030 , Pharmacology  
037 Drug Literature Index

LANGUAGE: English

CT Medical Descriptors:

animal experiment  
animal model  
clinical trial  
drug mechanism  
drug receptor binding  
endometriosis: DT, drug therapy

female  
fertilization in vitro  
follicleotropin release  
gonadotropin release  
gynecology  
hormone release

human  
human tissue  
intramuscular drug administration  
intranasal drug administration  
leiomyoma: DT, drug therapy  
luteinizing hormone release

male  
nonhuman  
ovary polycystic disease: . . .  
therapy

clomifene: DT, drug therapy  
clomifene: CM, drug comparison  
gonadorelin: EC, endogenous compound  
gonadorelin agonist: CM, drug comparison  
gonadorelin agonist: DT, drug therapy  
gonadorelin agonist: PD, pharmacology  
cetrorelix: CT, clinical trial  
cetrorelix: CM, drug comparison  
cetrorelix: DT, drug therapy  
cetrorelix: PD, pharmacology  
cetrorelix: CB, drug combination

human menopausal gonadotropin: PD, pharmacology  
human menopausal gonadotropin: CB, drug combination

RN (clomifene) 911-45-5; (gonadorelin) 33515-09-2, 9034-40-6; (

**cetrorelix** 120287-85-6; (human menopausal gonadotropin)

61489-71-2

CN Sb 75; **Cetrorelix**

L6 ANSWER 16 OF 21 USPATFULL

ACCESSION NUMBER: 1999:128511 USPATFULL  
TITLE: Pharmaceutical formulations for sustained drug delivery  
INVENTOR(S): Gefter, Malcolm L., Lincoln, MA, United States  
Barker, Nicholas, Southborough, MA, United States  
Musso, Gary, Hopkinton, MA, United States  
Molineaux, Christopher J., Brookline, MA, United States  
PATENT ASSIGNEE(S): Praecis Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5968895		19991019
APPLICATION INFO.:	US 1996-762747		19961211 (8)
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Richter, Johann		
ASSISTANT EXAMINER:	Delacroix-Muirheid, C.		
LEGAL REPRESENTATIVE:	Lahive & Cockfield, LLP, Mandragouras, Amy E., DeConti, Giulio A.		
NUMBER OF CLAIMS:	32		
EXEMPLARY CLAIM:	10		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	775		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Sustained delivery formulations comprising a water-insoluble complex of a peptide and a carrier macromolecule are disclosed. The formulations of the invention allow for loading of high concentrations of peptide in a small volume and for delivery of a pharmaceutically active peptide for prolonged periods, e.g., one month, after administration of the complex. The complexes of the invention can be milled or crushed to a fine powder. In powdered form, the complexes form stable aqueous suspensions and dispersions, suitable for injection. In a preferred embodiment, the peptide of the complex is an LHRH analogue, preferably an LHRH antagonist, and the carrier macromolecule is an anionic polymer, preferably carboxymethylcellulose. Methods of making the complexes of the invention, and methods of using LHRH-analogue-containing complexes to treat conditions treatable with an LHRH analogue, are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the luteinizing hormone releasing hormone receptor such that release of luteinizing hormone is inhibited. Examples of LHRH antagonists include Antide, **Cetrorelix**, compounds described in U.S. Pat. No. 5,470,947 to Folkers et al.; PCT Publication No. WO 89/01944 by Folkers et al.; . . .

DETD . . . include hormone-dependent cancers (including prostate cancer, breast cancer, ovarian cancer, uterine cancer and testicular cancer), benign prostatic hypertrophy, precocious puberty, **endometriosis**, uterine fibroids, infertility (through in vitro fertilization) and fertility (i.e., contraceptive uses).

DETD . . . hormone-dependent cancers, such as prostate cancer, breast cancer, ovarian cancer, uterine cancer and testicular cancer, benign prostatic hypertrophy, precocious puberty, **endometriosis** and uterine fibroids. Accordingly, the invention provides methods of treating these diseases and disorders by administering a pharmaceutical formulation of. . .

IT 9000-07-1D, Carrageenan, anionic derivs. 9004-32-4 9005-32-7, Alginate acid 9005-38-3, Algin 9034-40-6D, LHRH, analogs 9046-38-2, Polygalacturonic acid 9063-38-1, Sodium starch glycolate 11138-66-2, Xanthan gum 120287-85-6, **Cetrorelix** 183552-38-7, PPI 149 209122-72-5 209122-73-6  
(pharmaceutical formulations for sustained drug delivery of peptides)

L6 ANSWER 17 OF 21 USPATFULL

ACCESSION NUMBER: 1999:81921 USPATFULL  
TITLE: GnRH antagonists  
INVENTOR(S): Semple, Graeme, Hampshire, United Kingdom  
Jiang, Guangcheng, San Diego, CA, United States  
PATENT ASSIGNEE(S): Ferring BV, Hoofddorp, Netherlands (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5925730		19990720
APPLICATION INFO.:	US 1997-837042		19970411 (8)
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Hill, Jr., Robert J.		
ASSISTANT EXAMINER:	Delacroix-Muirheid, C.		
LEGAL REPRESENTATIVE:	Fitch, Even, Tabin & Flannery		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1458		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties. These antagonists may be used to regulate fertility and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. These antagonists have a derivative of aminoPhe or its equivalent in the 5- and/or 6-positions. This derivative contains a carbamoyl group or a heterocycle including a urea in its side chain. Particularly effective decapeptides, which continue to exhibit very substantial suppression of LH secretion at 96 hours following injection, have the formulae: Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, and Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Amf(Q.sub.2)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Q.sub.2 is Cbm or MeCbm.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of ovulation for in vitro fertilization. For example, GnRH antagonists may be used for the treatment of precocious puberty and **endometriosis** and other such conditions which result from hypersecretion of gonadotropins, and they are also useful for regulating the secretion of. . .

SUMM (10) interval treatment of **endometrial** cancer between diagnosis and surgery.

SUMM (3) **endometrial** cancer;

SUMM (7) **endometriosis**;

SUMM . . . improved GnRH antagonists has resulted in the making of Antide, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, Lys(Nic).sup.5, D-Lys(Nic).sup.6, ILys.sup.8, D-Ala.sup.10]-GnRH; and **Cetrorelix**, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, D-Cit.sup.6, D-Ala.sup.10]-GnRH. U.S. Pat. No. 5,516,887 describes GnRH antagonists which are said to be more. . .

SUMM . . . other modifications to the 5-position residue, or the 5- and 6-position residues, in this subclass of GnRH antagonists, which includes **Cetrorelix**, Antarelix, Acyline, Antide and others, unexpectedly result in compounds which when administered sc exhibit the particularly advantageous property of long. . .

SUMM . . . mammals, especially humans, as fertility regulators and for the treatment of pathological conditions such as precocious puberty, hormone-dependent neoplasia, dysmenorrhea, **endometriosis**, steroid-dependent tumors, and the other short-term and long-term indications mentioned hereinbefore. They are also useful diagnostically.

DETD The peptide [4Aph(Hor).sup.5, D-Cit.sup.6]-Antide, an analog of the peptide **Cetrorelix** having the formula Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-Cit-Leu-ILys-Pro-D-Ala-NH.sub.2 is synthesized using the synthesis as generally set forth in Example 1. Instead of coupling N.sup.alpha. . .

DETD The peptide is more hydrophilic than **Cetrorelix** and exhibits as long duration of bioactivity as **Cetrorelix** when tested in vivo for suppression of LH secretion as in Example 1. It has marginally better suppression at 3. . .

DETD . . . in Example 1. The peptide Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-Lys(Nic)-Leu-ILys-Pro-D-Ala-NH.sub.2 is obtained in the RP-HPLC purification. It is considered to be more hydrophilic than **Cetrorelix** and to exhibit as long duration of bioactivity as **Cetrorelix** for suppression of LH secretion.

L6 ANSWER 18 OF 21 USPATFULL

ACCESSION NUMBER: 1998:124554 USPATFULL  
 TITLE: GnRH antagonist decapeptides  
 INVENTOR(S): Jiang, Guangcheng, San Diego, CA, United States  
 Semple, Graeme, Hampshire, United Kingdom  
 PATENT ASSIGNEE(S): Ferring BV, Hoofddorp, Netherlands (non-U.S.)

corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5821230		19981013
APPLICATION INFO.:	US 1997-837041		19970411 (8)
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Tsang, Cecilia J.		
ASSISTANT EXAMINER:	Wang, Cecilia F.		
LEGAL REPRESENTATIVE:	Fitch, Even, Tabin & Flannery		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1630		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties and/or which can be synthesized more economically. These antagonists may be used in the same manner as the compounds of which they are analogs to regulate fertility and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. One particularly effective peptide, a decapeptide analog of the GnRH antagonist Acyline, has the formula: Ac-D-2Nal-D-4Cpa-D-Dpr(methylcarbamoyl)-Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2. It continues to exhibit very substantial suppression of LH secretion at 96 hours following injection. Other economically attractive and pharmacologically effective analogs have the formulas: Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2 ; and Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(hydroxotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Xaa.sub.3 is D-Gln or Gln.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of ovulation for in vitro fertilization. For example, GnRH antagonists may be used for the treatment of precocious puberty and **endometriosis** and other such conditions which result from hypersecretion of gonadotropins, and they are also useful for regulating the secretion of. . .

SUMM (10) interval treatment of **endometrial** cancer between diagnosis and surgery.

SUMM (3) **endometrial** cancer;

SUMM (7) **endometriosis**;

SUMM . . . improved GnRH antagonists has resulted in the making of Antide, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, Lys(Nic).sup.5, D-Lys(Nic).sup.6, ILys.sup.8, D-Ala.sup.10]-GnRH; and **Cetrorelix**, i.e. [Ac-D-2Nal.sup.1, D-4ClPhe.sup.2, D-3Pal.sup.3, D-Cit.sup.6, D-Ala.sup.10]-GnRH. U.S. Pat. No. 5,516,887 describes GnRH antagonists which are said to be more. . .

SUMM . . . of less expensive residues, the cost can be reduced without reducing biopotency or this subclass of GnRH antagonists which includes **Cetrorelix**, Antarelix, Acyline, Azaline B, Antide and others. Not only are these analogs less expensive to synthesize than peptides containing the. . .

SUMM . . . mammals, especially humans, as fertility regulators and for the treatment of pathological conditions such as precocious puberty, hormone-dependent neoplasia, dysmenorrhea, **endometriosis**, steroid-dependent tumors, and the other short-term and long-term indications mentioned hereinbefore. They are also useful diagnostically.

DETD An analog of the peptide **Cetrorelix** having the formula Ac-D-2Nal-D-4Cpa-D-Dpr(methylcarbamoyl)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH.sub.2 is synthesized using the synthesis as generally set forth in Example 1. Instead of coupling N.sup..alpha.. . .

DETD . . . is considered to be more hydrophilic than Acyline and to have longer duration of in vivo suppression of LH than **Cetrorelix**.

L6 ANSWER 19 OF 21 USPATFULL

ACCESSION NUMBER: 1998:98932 USPATFULL

TITLE: DHA-pharmaceutical agent conjugates of taxanes

INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States  
Swindell, Charles S., Merion, PA, United States  
Webb, Nigel L., Bryn Mawr, PA, United States  
Bradley, Matthews O., Laytonsville, MD, United States

PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States  
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5795909		19980818
APPLICATION INFO.:	US 1996-651312		19960522 (8)
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Jarvis, William R. A.		
LEGAL REPRESENTATIVE:	Wolf, Greenfield & Sacks, P.C.		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	27 Drawing Figure(s); 14 Drawing Page(s)		
LINE COUNT:	2451		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosaehaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. endometriosis, ovarian cysts, etc.) and as contraceptive agents. . . Other conditions treatable according to the invention will be apparent to those skilled. . .

DETD . . . canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; **cetrorelix**; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; . . .

DETD . . . treating diabetes and its complications, excess acid secretion, cardiovascular conditions involving cholesterol (e.g., hyperlipidemia and hypercholesterolemia), diarrhea, ovarian diseases (e.g. endometriosis, ovarian cysts, etc.) and as contraceptive agents.

L6 ANSWER 20 OF 21 USPATFULL

ACCESSION NUMBER: 1998:75185 USPATFULL  
 TITLE: Long-acting injection suspensions and a process for their preparation  
 INVENTOR(S): Engel, Jurgen, Alzenau, Germany, Federal Republic of  
 Klokke-Bethke, Karin, Lenggries, Germany, Federal Republic of  
 Reissman, Thomas, Frankfurt, Germany, Federal Republic of  
 Hilgard, Peter, Frankfurt, Germany, Federal Republic of  
 PATENT ASSIGNEE(S): Asta Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5773032		19980630
APPLICATION INFO.:	US 1996-661017		19960610 (8)
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Azpuru, Carlos A.		
LEGAL REPRESENTATIVE:	Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP		
NUMBER OF CLAIMS:	8		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)		
LINE COUNT:	373		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Poorly soluble salts of LHRH analogues, for example **cetrorelix** embonate, display an intrinsic sustained release effect in the grain size 5 .mu.m to 200 .mu.m.

SUMM . . . analogs are understood to be both superagonists such as goserelin (INN) or triptorelin (INN), as well as antagonists such as **cetrorelix** (INN), antide (INN) or ganirelix (INN). Goserelin, and the synthesis of goserelin, is described in Drugs of the Future, 5. . .

SUMM . . . flare up, which has to be counteracted with additional medication. In contrast, in the case of the antagonists of which **cetrorelix** (INN) is one, the pharmacological effect occurs

immediately and there is no flare up. Lasting reduction in the sex hormone. . . of prostate carcinoma and mamma carcinoma to reduce tumour growth in sex hormone-dependent tumours and also a curative treatment in **endometriosis**. Chemically speaking, the LHRH-superagonists and the antagonists are nona- or decapeptides.

SUMM An LHRH antagonist that is effective in the above indication is **cetrorelix**, a decapeptide of the amino acid sequence Ac-DNal-DpCl-Phe-DPal-Ser-Tyr-DCit-Leu-Arg-Pro-D-Ala-NH.sub.2. Its synthesis and pharmacological properties are described in EP 299 402. **Cetrorelix** acetate has been identified as the physiologically acceptable salt. It was found in preclinical and clinical studies that the aqueous solution of **cetrorelix** acetate had to be applied daily in order to lower the hormone level of testosterone or oestradiol to the appropriate. . .

SUMM DE-OS 42 23 282.1 describes the preparation of a sustained release formulation of **cetrorelix** embonate by microencapsulation. Implants are medicinal forms permitting longer intervals of use. For example, when implanted under the skin, a. . .

DRWD FIG. 2 Effect of administration of **Cetrorelix**, 0.5 mg/kg s.c. on testosterone levels in male rats. D20762 (in situ) precipitate without viscous additives.

DRWD FIG. 3 Effect of administration of **Cetrorelix**, 0.5 mg/kg s.c. on testosterone levels in male rats. D-20762 Microparticles RCSES 91-08.

DETD . . . the tumour weight for the untreated control animals shows uninhibited increase. Curves 1 (\*) and 2 (0) show treatment with **cetrorelix** acetate in two different carriers. The extended curve 3 shows the drastic reduction in tumour weight after embonate treatment.

DETD The formulation of the invention is an X-ray amorphous precipitate of the decapeptide **cetrorelix** as an embonic acid salt. The aqueous suspension of this precipitate, which may optionally contain isotonifying additives, showed a marked. . .

DETD . . . to be amorphous. The particle size of the formulation of the invention lies between 5  $\mu$ m and 200  $\mu$ m. A **cetrorelix** embonate with a particle size under 5  $\mu$ m showed a sustained release effect inferior to that of the formulation of the invention. Similarly, a **cetrorelix** embonate with a particle size of more than 200  $\mu$ m showed a poorer sustained release effect than the formulation of. . .

DETD . . . free base) to embonic acid, an aqueous solution of embonic acid containing alkali in excess is combined with the acetate **cetrorelix** acetate solution, embonic acid precipitating as yellow crystals. On addition of dilute sodium hydroxide solution up to pH 7-7.5, the embonic acid dissolves and precipitates with the decapeptide as aqueous **cetrorelix** embonate salt of the molar composition peptide: embonic acid 2:1 (Mol/Mol). The precipitate is filtered off, washed with H.sub.2O. . .

DETD **Cetrorelix** acetate and embonic acid are dissolved in equimolar proportions in dimethylacetamide and the solution is dropped into water. The white precipitate of the **cetrorelix** embonate peptide: embonic acid 2:1 (Mol/Mol) is filtered off and dried.

DETD **Cetrorelix** and embonic acid are dissolved in a molar ratio of 1:1.6 in a mixture of dimethyl acetamide and optionally water. . .

DETD Suspensions of the precipitates were applied subcutaneously to male rats in the dose 0.5 mg **cetrorelix**/kg body weight and determined after application as a measure of the effect of the peptide on testosterone plasma levels. The effect of the **cetrorelix** consists in reduction of the testosterone level. As a reference an injection suspension was tested as well, that prepared according. . . the peptide embonate in poly(lactic acid, glycolic acid) copolymers. The duration of action of a non-sustained release dosage form of **cetrorelix** was determined via examination of the aqueous solution of **cetrorelix** acetate.

DETD . . . the course of the testosterone level over 300 h determined in male rats after application of the aqueous solution of **cetrorelix** acetate (D-20761). The effect of testosterone suppression is achieved 6 h after the application. Suppression under 1 ng/ml could still. . .

DETD FIG. 2 shows the testosterone level over 300 h in four animals (No. 11-14) after applying the same dose of **cetrorelix** as a suspension of **cetrorelix** embonate (D-20762) without viscous additives prepared according to Example 1 (D-20762). The testosterone suppression is also achieved 6 h after. . .

CLM What is claimed is:

. . . particles lies between 5 and 200  $\mu$ m, characterized in that the

LHRH analogue is selected from the group consisting of **Cetrorelix**, antarelix, ganirelix, antide and A-75998 which is not in the form of particles or microcapsules of a homopolymer or copolymer.

L6 ANSWER 21 OF 21 USPATFULL

ACCESSION NUMBER: 97:78416 USPATFULL

TITLE: Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases

INVENTOR(S): Engel, Jurgen, Alzenau, Germany, Federal Republic of  
Hilgard, Peter, Frankfurt, Germany, Federal Republic of  
Reissmann, Thomas, Frankfurt, Germany, Federal Republic of

PATENT ASSIGNEE(S): ASTA Medica Aktiengesellschaft, Dresden, Germany,  
Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5663145		19970902
APPLICATION INFO.:	US 1994-354838		19941208 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1993-4342091	19931209
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Russel, Jeffrey E.	
LEGAL REPRESENTATIVE:	Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP	
NUMBER OF CLAIMS:	25	
EXEMPLARY CLAIM:	7	
LINE COUNT:	227	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB For application during the treatment of benign and malign tumour diseases, the product according to the invention containing the initial dose of **Cetrorelix** acetate and one or more maintenance doses of **Cetrorelix** acetate, **Cetrorelix** embonate or a slow-release form of **Cetrorelix**, is used as a combination preparation for treatment to be administered at specific time intervals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases

DETD **Cetrorelix** (INN) is an antagonist for LHRH. The mode of action is completely different from that of the known superagonists. Synthesis. . . few important pharmacological effects are described in EP 299 402. This indicates that different doses are required for treatment with **Cetrorelix**.

DETD . . . purposes are initially placed in another glass vessel and 91.17 g of acetic acid are added. The calculated amount of **Cetrorelix** acetate (1.62-1.695 g. depending on the concentration of the feedstock used) is dissolved with stirring in the prepared 30% strength. . .

DETD . . . size 0.2 .mu.m, under aseptic conditions). The first 100 ml are discarded. The filters are sterilised with steam under pressure. **Cetrorelix** solution for freeze-drying is stored under protection against recontamination. The solution is immediately metered into DIN 2R injection vials which. . .

DETD **Cetrorelix** lyophilisate 1 mg is a white, solid freeze-dried cake in a colourless 2 ml injection phial which is sealed with. . .

DETD An aqueous solution of embonic acid containing excess alkali is combined with the acetic acid **Cetrorelix** acetate solution at an equimolar ratio of peptide (calculated as free base) to embonic acid, wherein the embonic acid precipitates. . . caustic soda solution until the pH is 7-7.5, the embonic acid dissolves and precipitates with the decapptide as a white **Cetrorelix** embonate salt with the molar composition peptide:embonic acid of e.g. 2:1 (mol/mol). The precipitate is filtered off, washed with H.sub.2O. . .

DETD A container or several containers are filled with the initial dose of **Cetrorelix** acetate lyophilisate. The amount used is between 1 mg and 60 mg of lyophilisate per container.

DETD Up to 30 further containers are filled with the maintenance dose of **Cetrorelix** acetate lyophilisate. The amount used is between 0.1 and 30 mg per container.

CLM

What is claimed is:

3. The kit of claim 1, wherein the LHRH antagonist is **Cetrorelix**.
4. The kit of claim 3, wherein the initial dose of **Cetrorelix** is between about 1 and about 60 mg.
5. The kit of claim 3, wherein the maintenance dose of **Cetrorelix** is between about 0.1 and about 60 mg.
6. The kit of claim 3, wherein the maintenance dose of **Cetrorelix** consists of a slow-releasing formulation.
9. The method of claim 7, wherein the LHRH antagonist is **Cetrorelix**.
10. The method of claim 7, wherein **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.
11. The method of claim 9, wherein the initial dose of **Cetrorelix** is between about 1 and about 60 mg, and the maintenance dose of **Cetrorelix** is between about 0.1 and about 30 mg.
12. The method of claim 11, wherein the **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.
14. The method of claim 7, wherein the hormone-dependent condition is **endometrial hyperplasia**.
22. The method of claim 21, wherein the LHRH antagonist is **Cetrorelix**.
23. The method of claim 21, wherein the **Cetrorelix** of the maintenance dose consists of a slow-releasing formulation.
24. The method of claim 22, wherein the initial dose of **Cetrorelix** is between about 1 and 60 mg, and the maintenance dose of **Cetrorelix** is between about 0.1 and 30 mg.
25. The method of claim 24, wherein the **Cetrorelix** of the maintenance dose comprises **Cetrorelix** pamoate or **Cetrorelix** acetate in a slow-releasing form.

IT 120287-85-6, Cetrorelix 145672-81-7 145672-82-8  
(combined package for application of high initial doses of cetrorelix and lower maintenance doses)